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**High-dose chemotherapy (HDCT) with hematopoietic stem cell transplantation (HSCT) in high-risk breast cancer (BC) patients with  $\geq 4$  involved axillary lymph nodes (ALN): 20-year follow-up of a randomized phase 3 study**

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**Background:** Adjuvant HDCT for high-risk BC is not beneficial overall compared to conventional chemotherapy at the cost of considerable toxicity. HDCT benefit, however, may be present in very high-risk patients (i.e.  $>9$  involved ALN) and in triple negative (TN) BC patients, although long-term results are lacking for most initial studies. We evaluated long-term outcome of a randomized phase 3 study, conducted from 1993 to 99.

**Methods:** Patients aged  $<56$  years with early BC and  $\geq 4$  involved ALN were randomized to either conventional chemotherapy or HDCT as adjuvant systemic treatment. The conventional arm consisted of 5x fluorouracil, epirubicin and cyclophosphamide (FEC) 3-weekly. In the HDCT arm, the 5<sup>th</sup> FEC was replaced by cyclophosphamide 6000 mg/m<sup>2</sup>, thiotepa 480 mg/m<sup>2</sup>, carboplatin 1600 mg/m<sup>2</sup> and supported with autologous HSCT (Rodenhuis, NEJM 2003). We collected 20-year follow-up data from medical records, general practitioners, and the Netherlands Cancer Registry. Endpoints were relapse free survival (RFS), overall survival (OS), BC specific survival (BCSS), and safety based on intention to treat analyses.

**Results:** 885 patients (64% 4-9 ALN, 36%  $>9$  ALN; 53% ER+/HER2-, 23% HER2+, 16% TN, 8% unknown) were randomized to FEC (n = 443) or HDCT (n = 442). The table shows efficacy results of univariable Cox models. With 20 years median follow-up, relapse or death occurred in 272 patients (61%) who received FEC vs in 257 (58%) HDCT patients (HR 0.88; 95% CI 0.74-1.05). The effect of HDCT compared to FEC was most pronounced in patients with  $>9$  involved ALN and in TNBC patients. In 138 TNBC patients the 20-year OS estimate was 52% after HDCT vs 39% after FEC. Long-term safety and BCSS will also be presented at the meeting.

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RFS	HDCT			FEC			HR	95% CI	p
	N	20 yr (%)	95% CI	20 yr (%)	95% CI				
All	885	42	37-47	38	33-43	0.88	0.74-1.05	0.15	
4-9 ALN	568	43	38-50	44	38-50	1.00	0.81-1.25	0.97	
$>9$ ALN	317	39	31-47	27	21-36	0.71	0.54-0.94	0.02	
ER+/HER2-	469	40	34-47	36	30-43	0.83	0.66-1.04	0.11	
HER2+	205	38	30-49	42	33-52	1.15	0.80-1.63	0.46	
TN	138	51	40-65	34	24-48	0.66	0.42-1.03	0.07	
OS		HDCT		FEC					
	N	20 yr (%)	95% CI	20 yr (%)	95% CI	HR	95% CI	p	
All	885	45	41-50	41	37-46	0.89	0.74-1.06	0.18	
4-9 ALN	568	46	40-52	48	42-54	1.01	0.81-1.27	0.91	
$>9$ ALN	317	44	37-53	30	23-38	0.72	0.54-0.95	0.02	
ER+/HER2-	469	46	40-53	40	34-47	0.81	0.64-1.03	0.09	
HER2+	205	40	32-51	46	37-56	1.15	0.80-1.66	0.44	
TN	138	52	41-65	39	29-52	0.71	0.45-1.12	0.14	

**Conclusions:** Long-term follow-up confirms survival benefit of HDCT in BC patients with  $>9$  involved ALN and suggests benefit in TNBC patients.

**Clinical trial identification:** NCT03087409.

**Legal entity responsible for the study:** High-risk breast cancer study group from the Netherlands Working Party on Autologous Transplantation in Solid Tumors.

**Funding:** Has not received any funding.

**Disclosure:** T.G. Steenbruggen: Financial support: Memidis Pharma unrelated to the submitted work. V.C.G. Tjan-Heijnen: Research funding through grants institution: Eisai, Roche, Pfizer, Novartis, and AstraZeneca; Compensation for service as a consultant: AstraZeneca, Pfizer, Novartis, and Roche; Honoraria: Pfizer, Roche, and Novartis; Travel expenses: Pfizer, Novartis, and Roche. S.C. Linn: Institutional research funding: AstraZeneca, Amgen, BMS, Genentech, Roche, and Sanofi; Advisory board member: AstraZeneca, Novartis, Roche and Sanofi. E.G.E. de Vries: Consulting/advisory board fees: Synthon, Pfizer and Sanofi; Grants: Novartis, Amgen, Roche/Genentech, Regeneron, Chugai, Synthon, AstraZeneca, Radius Health, CytomX Therapeutics and Nordic Nanovector, all to the hospital and unrelated to the submitted work. G.S. Sonke: Institutional research funding: AstraZeneca, Merck, Novartis, Roche, unrelated to the submitted work. All other authors have declared no conflicts of interest.